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Development of Novel Medications for Drug Addiction

The Legacy of an African Shrub

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ABSTRACT: Ibogaine, one of several alkaloids found in the root bark of the African shrub *Tabernanthe iboga*, has been claimed to be effective in treating multiple forms of drug abuse. Problems associated with side effects of ibogaine have spawned a search for more effective and safer structural derivatives. 18-Methoxycoronaridine (18-MC), a novel iboga alkaloid congener, appears to have substantial potential for broad use as an anti-addictive therapy. Like ibogaine (40 mg/kg), 18-MC (40 mg/kg) decreases the intravenous self-administration of morphine and cocaine and the oral self-administration of ethanol and nicotine in rats; unlike ibogaine, 18-MC does not affect responding for a non-drug reinforcer (water). Ibogaine and 18-MC appear to reduce the reinforcing efficacies, rather than the potencies, of drugs of abuse. Both ibogaine and 18-MC decrease extracellular levels of dopamine in the nucleus accumbens while only ibogaine increases serotonin levels in this brain region. Both ibogaine and 18-MC block morphine-induced and nicotine-induced dopamine release in the accumbens; only ibogaine enhances cocaine-induced increases in dopamine levels. Ibogaine produces whole body tremors and, at high doses (at least 100 mg/kg), cerebellar damage; 18-MC does not produce these effects. Ibogaine, but not 18-MC, causes bradycardia at high doses. Ibogaine and its metabolite noribogaine have low μ M affinities for κ and μ opioid receptors, NMDA receptors, 5HT-3 receptors, sigma-2 sites, sodium channels and the serotonin transporter. 18-MC has low μ M affinities at all three opioid receptors and at 5HT-3 receptors but much lower or no affinities for NMDA and sigma-2 receptors, sodium channels, and the 5HT transporter. Both 18-MC and ibogaine are sequestered in fat and, like ibogaine, 18-MC probably has an active metabolite. 18-MC also has (+) and (–) enantiomers, both of which are active. Considered together, all of the data indicate that 18-MC should be safer than ibogaine and at least as efficacious as an anti-addictive medication.

INTRODUCTION

It would indeed be remarkable if one or only a few treatments with a new agent attenuated or abolished an individual's addiction to drugs for a prolonged period of time. Claims that the naturally occurring substance ibogaine had such effects were

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intriguing, enough so to spawn research programs in several institutions. Ibogaine is one of several alkaloids found in the root bark of the African shrub *Tabernanthe iboga*. Extracts of iboga have a long history of use, principally as a stimulant to keep African hunters awake and motionless while stalking prey but also as part of initiation rites and religious rituals of Bwiti and Mbiri cults. Studies conducted in France in the early 1900's indicated that ibogaine had hallucinogenic as well as stimulant properties. Although never widespread in this country, ibogaine's appearance on the illicit market in the 1960's caused the FDA in 1970 to classify it as a Schedule I substance. Five United States patents (numbers 4,499,096; 4,587,243; 4,857,523; 5,026,697; 5,124,994) issued between 1985 and 1992 addressed ibogaine's potential anti-addictive properties; it was claimed to be effective in treating opiate (heroin) addiction, stimulant (cocaine and amphetamine) abuse, alcohol dependence, cigarette smoking (nicotine dependence), and poly-drug abuse. Ibogaine supposedly interferes with the "physiological and psychological aspects" of addiction, abolishing the craving for drugs. According to the patents, a single treatment may be effective for six months and a series of four treatments may be effective for up to three years. Studies in animals have, to a limited extent, corroborated these claims. In rats ibogaine has been reported to decrease intravenous morphine¹ and cocaine^{2,3} self-administration as well as oral intake of alcohol⁴ and nicotine.⁵ Most of these effects last for a day or more after ibogaine treatment, well beyond the presence of the drug, or its active metabolite noribogaine, in the brain.^{6,7}

Reports of side effects of ibogaine have limited its potential therapeutic utility and have seriously hampered efforts to develop ibogaine as a FDA-approved medication. Aside from having stimulant and hallucinogenic properties, ibogaine induces tremors, manifested as whole body shaking in rats. The tremors are attributable to activation of an olivo-cerebellar pathway⁸ and, in rats, occur in response to moderate doses (20–40 mg/kg); the tremors are reduced after high doses (≥ 100 mg/kg) which, apparently by overstimulating cerebellar Purkinje cells,^{9–11} produce damage to the cerebellar vermis. Another side effect which is not as well documented¹² but may have more clinical significance is a pronounced bradycardia (decrease in heart rate).

The problems associated with ibogaine led to attempts to develop a safer and still efficacious structural derivative. It was Sydney Archer, in fact, who introduced Martin Kuehne, a medicinal chemist, to Stanley Glick, a neuropharmacologist, and suggested they collaborate. Dr. Kuehne's expertise on *vinca* alkaloids, structural relatives of *iboga* alkaloids, was a perfect fit with Dr. Glick's interest in ibogaine and related anti-addictive agents.

Initial work with other *iboga* alkaloids demonstrated that decreases in drug self-administration could be dissociated from tremorigenic activity: R-ibogamine and R-coronaridine, two non-tremorigenic *iboga* alkaloids (FIG. 1), mimicked ibogaine's effects on morphine and cocaine self-administration.¹³ But, like ibogaine, these other alkaloids also had acute nonspecific effects, reducing responding for a non-drug reinforcer (water) as well as responding for drugs during the first 1–2 hours after administration. Several synthetic analogues of ibogamine and coronaridine had similar profiles of activity. However, 18-methoxycoronaridine (18-MC; FIG. 1) was different: this non-tremorigenic *iboga* alkaloid congener mimicked ibogaine's effects on morphine and cocaine self-administration but had no acute depressant effect on responding for water. Further studies showed that 18-MC also reduced alcohol and

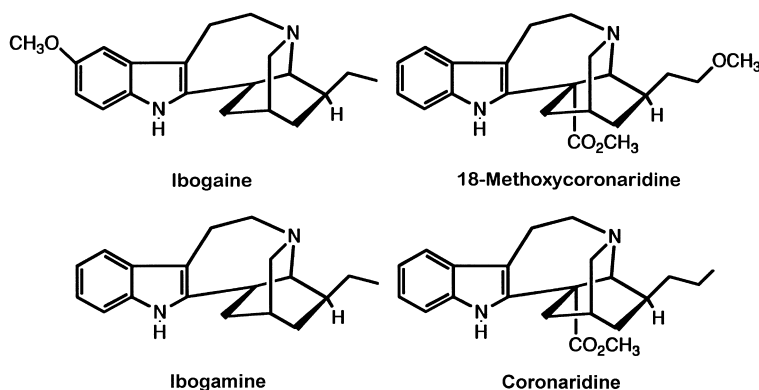


FIGURE 1. Iboga alkaloid and congener structures.

nicotine intake and produced no cerebellar toxicity. This paper will review these and other studies, particularly those that distinguish 18-MC from ibogaine.

MATERIALS AND METHODS

Animals

All subjects were naive female Sprague-Dawley (Taconic) or Long-Evans (Charles River) rats, approximately 3 months old and weighing 230–250 g at the beginning of an experiment. Rats were maintained on a normal light/dark cycle (lights on/off at 0700 h/1900 h).

Drug Self-Administration

The intravenous self-administration procedure has been described previously.^{1,3,13} Briefly, responses on either of two levers (mounted 15 cm apart on the front wall of each operant test cage) were recorded on an IBM-compatible 486 computer with a Med Associates, Inc. interface. The intravenous self-administration system consisted of polyethylene-silicone cannulas constructed according to the design of Weeks,¹⁴ Instech harnesses and commutators, and Harvard Apparatus infusion pumps (#55-2222). Shaping of the bar-press response was initially accomplished by training rats to bar-press for water. Cannulas were then implanted in the external jugular vein according to procedures described by Weeks.¹⁴ Self-administration testing began with a 16-h nocturnal session followed by daily 1-h sessions, 5 days (Monday–Friday) a week. A lever-press response produced a 10 or 50 μ l infusion of drug solution, 0.01 mg morphine sulfate or 0.1 mg cocaine hydrochloride, respectively, in 0.2–1.0 second. Since all rats generally weighed 250 ± 20 g, each response delivered approximately 0.04 mg/kg of morphine or 0.4 mg/kg cocaine.

Nicotine was self-administered via the oral route using an operant procedure previously described.¹⁵ Two fluid delivery systems, each consisting of a fluid container connected to a solenoid, delivered 0.1 ml nicotine solution or water to stainless steel drinking cups located above each of two levers. An aqueous solution of nicotine bitartrate was made at a concentration of 4 µg/ml (1.4 µg/ml of the base); the solution was adjusted to a pH of 7.0. Rats were initially placed into the operant chambers overnight and trained to respond for water, using both levers, on a continuous reinforcement schedule. Following nocturnal training, rats were switched to 1-hour sessions during the day, five days a week (Monday–Friday), and maintained on a 23-hour water deprivation schedule. Rats were provided *ad libitum* access to water after test sessions on Fridays, with the water deprivation schedule reinstated on Sundays in preparation for Mondays' test sessions. After five consecutive daily sessions in which rats made at least 50 responses/hour, nicotine was introduced. Rats received nicotine by pressing one lever and water by pressing the other. Side of presentation of nicotine was alternated each day.

Locomotor Activity

Locomotor activity was assessed using cylindrical photocell activity cages (60 cm, three crossing beams) interfaced to an IBM-compatible 486 computer.¹⁶ Interruptions of light beams were recorded with the software Med-PC (MED Associates, St. Albans, VT).

In Vivo Microdialysis

The microdialysis procedures used to assess effects of drug treatments on extracellular levels of dopamine and its metabolites have been used extensively in this laboratory.^{3,13,17–19} Briefly, under pentobarbital anesthesia, rats were implanted stereotactically with guide cannulas so that, when inserted, the tips of the dialysis probes would be located in the intended brain areas (e.g., nucleus accumbens, striatum, medial prefrontal cortex). Each cannula was fixed firmly in the skull with dental cement.

At least four days after surgery, a rat was placed in a dialysis chamber, a cylindrical (30 cm diameter) Plexiglas cage providing free access to food and water. The probe (2 or 3 mm; CMA) was then lowered into the guide cannula. The dialysis probe was continuously perfused with a solution containing 146 mM NaCl, 2.7 mM KCl, 1.2 mM CaCl₂ and 1.0 mM MgCl₂ at a flow rate of 1 µl/min. On the next morning (15–20 hours later), the dialysis experiment was carried out on a freely moving animal. Twenty minute fractions were collected in vials containing 2 µl of 1.1 N perchloric acid solution (containing 5 mg/l EDTA and 5 mg/l sodium metabisulfite). Upon completion of an experiment, rats were killed and histological analysis of each brain was performed to verify the locations of the probes.

Perfusate samples were analyzed by HPLC with electrochemical detection. The HPLC consisted of a Waters pump (model 510), a WISP autosampler (model 712), a Phase Separation Spherisorb C-18 column (S3 ODS2; 10 cm × 4.6 mm) and a Waters detector (model 464). The mobile phase consisted of 6.9 g/l sodium monobasic phosphate, 450 mg/l heptane sulfonic acid, 80 mg/l disodium EDTA, and 110 ml/l methanol; the solution was adjusted with HCl to pH 3.7 and was pumped at a rate of

1.2 ml/min. Chromatograms were processed using Hewlett-Packard HPLC 2D Chem Station software.

RESULTS

FIGURE 2 shows that, when administered acutely, 18-MC and ibogaine are approximately equally effective and equally potent in decreasing both morphine and cocaine self-administration. However, in contrast, ibogaine decreases responding for water to a similar extent while 18-MC has no effect. These data were the first indication that 18-MC might be more selective, and potentially more acceptable, than ibogaine as an anti-addictive therapy. There was even a suggestion that, at least on morphine self-administration, 18-MC might have longer lasting effects than

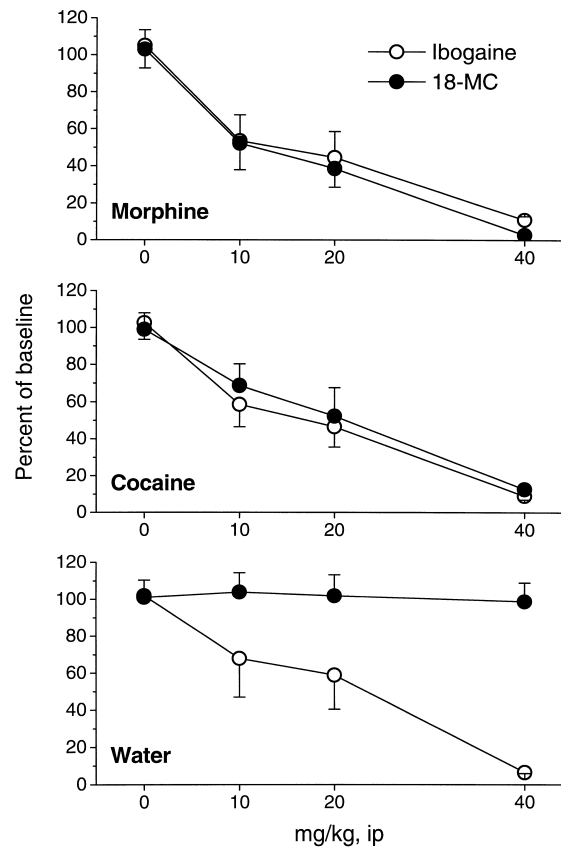


FIGURE 2. Acute dose-related effects of ibogaine and 18-MC on intravenous morphine and cocaine self-administration and on responding for water.

ibogaine (FIG. 3). In individual animals, both drugs have been observed to produce effects lasting for several days or, occasionally, even weeks.^{1,13}

Both ibogaine and 18-MC reduce preferences for alcohol in a two-bottle choice procedure^{20,21} and for oral nicotine in a two-lever operant procedure.⁵ In both paradigms, the effects of 18-MC appear to be more selective than the effects of ibogaine in that 18-MC, but not ibogaine, can reduce alcohol and nicotine intake without affecting water intake. 18-MC also seems to be approximately twice as potent as ibogaine in decreasing nicotine preferences (FIG. 4). Recent work with an intravenous nicotine self-administration paradigm suggests that 18-MC is at least twice as potent in decreasing nicotine intake as in decreasing either morphine or cocaine intake.

Exactly how 18-MC and ibogaine might alter sensitivity to a self-administered drug was, until recently, not clear. Because the self-administration dose-response curve is non-monotonic, its shape resembling an inverted U,^{22,23} a decrease in morphine intake, for example, could result from either antagonism or enhancement of morphine's actions. If 18-MC behaved as an opioid antagonist, it would be predicted that the unit infusion dose-response curve for self-administered morphine would be shifted to the right and the decrease in apparent potency of morphine would be

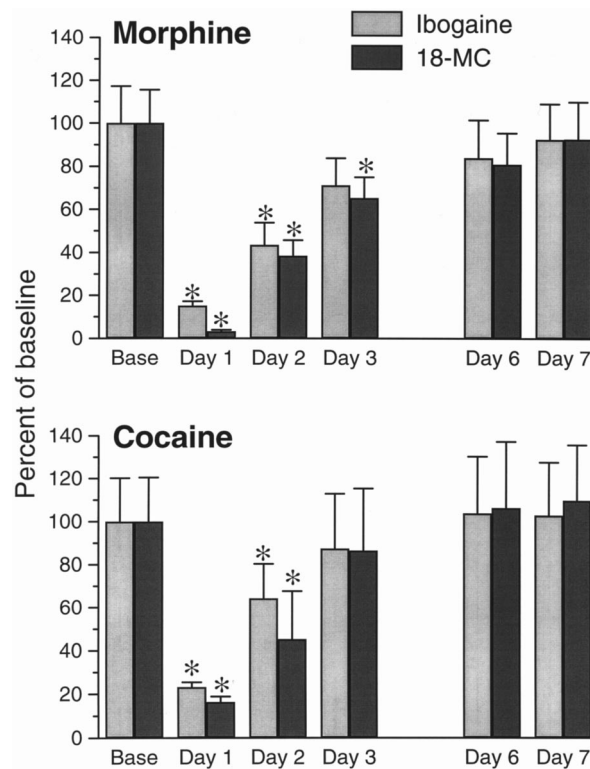


FIGURE 3. Aftereffects of ibogaine and 18-MC (both 40 mg/kg, i.p., administered before testing on Day 1) on morphine and cocaine self-administration.

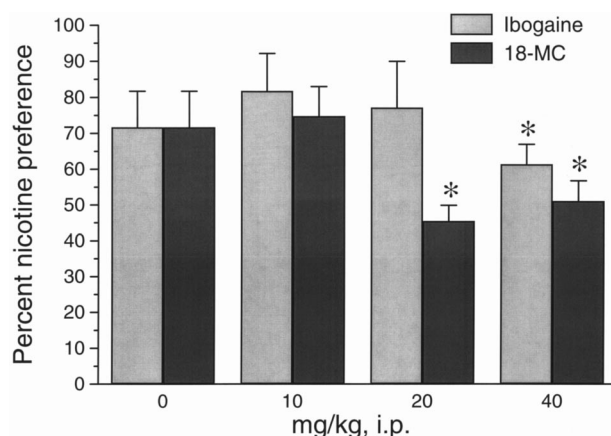


FIGURE 4. Acute effects of ibogaine and 18-MC on preferences (nicotine vs. water) for orally self-administered nicotine.

reflected as decreased responding for low unit infusion doses and increased responding for high unit infusion doses of morphine. If 18-MC behaved as an opioid agonist, just the opposite result, a shift of the morphine dose-response curve to the left, would be expected. However, as shown in FIGURE 5, 18-MC produces a downward shift in the dose-response curve for morphine self-administration; rather than altering the potency of morphine, 18-MC appears to decrease the efficacy of morphine to function as a reinforcer.²⁴ Stated another way, morphine seems to be simply less

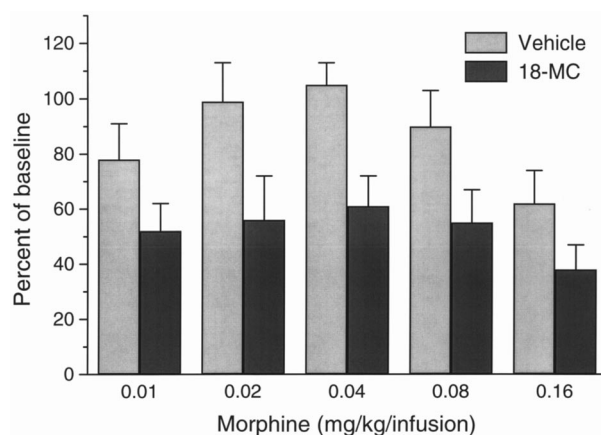


FIGURE 5. Acute effects of 18-MC (40 mg/kg, p.o.) on morphine self-administration at different unit infusion dosages.

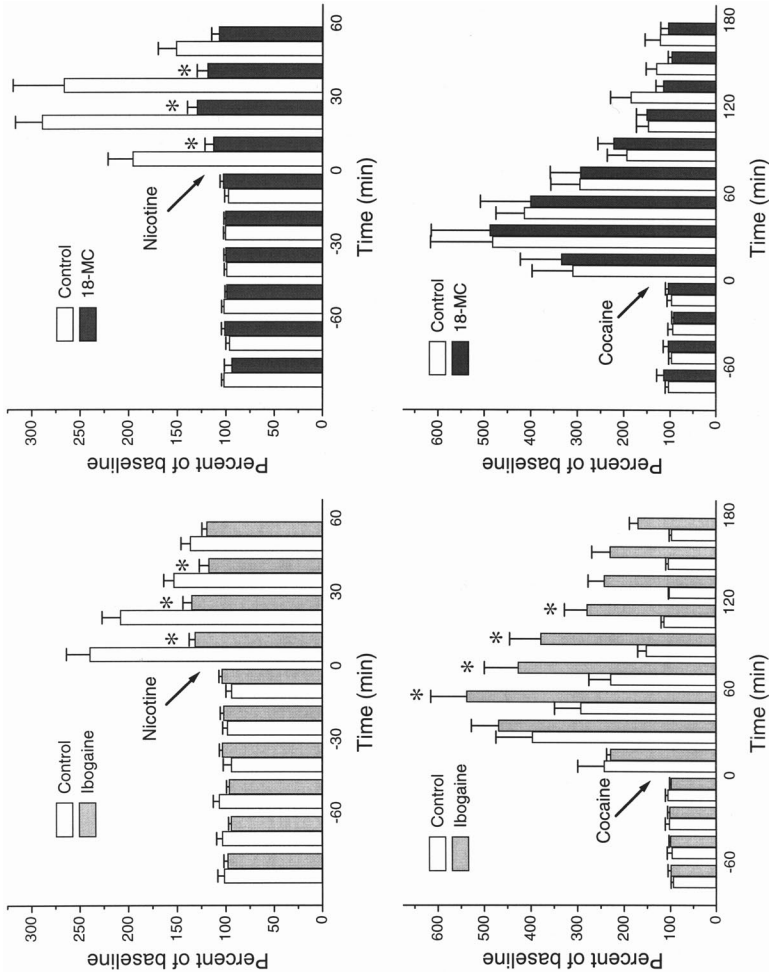


FIGURE 6. Effects of ibogaine and 18-MC pretreatment (both 40 mg/kg, i.p., administered 19 hours beforehand) on nicotine-induced (0.32 mg/kg, i.v.) and cocaine-induced (20 mg/kg, i.p.) increases in extracellular levels of dopamine in the nucleus accumbens.

reinforcing in the presence of 18-MC. Whether a similar statement is applicable to other drugs of abuse remains to be determined.

The mesolimbic dopaminergic pathway, originating in the ventral tegmental area and innervating the nucleus accumbens (NAC), appears to be critically involved in mediating the reinforcing effects of drugs of abuse. Increased extracellular levels of dopamine in the NAC occur in response to opioids, stimulants, ethanol and nicotine.²⁵ Conversely, consistent with their potential anti-addictive actions, both 18-MC¹³ and ibogaine¹⁸ acutely (within the first three hours of administration) decrease dopamine release in the NAC. Furthermore, at longer post-treatment intervals, when basal dopamine levels in the NAC are back to normal, both 18-MC and ibogaine interfere with drug-induced increases in NAC dopamine. Thus 18-MC pretreatment (19 hours beforehand), like ibogaine pretreatment, blocks morphine-induced^{18,24} and nicotine-induced^{5,19} dopamine release in the NAC. In contrast, however, ibogaine enhances cocaine-induced increases in NAC dopamine²⁶ whereas 18-MC has no effect (FIG. 6). These results suggest that the mechanisms of action of 18-MC and ibogaine are somewhat different and that different mechanisms underlie their behavioral interactions with opioid vs. stimulant drugs. Perhaps related to this are findings regarding serotonin: whereas ibogaine as well as noribogaine increase extracellular levels of serotonin in the NAC, 18-MC has no effect.²⁷ Lastly, in this context, it should be noted that 18-MC has (+) and (–) enantiomers. While both enantiomers decrease morphine self-administration (FIG. 7), only the (+) enantiomer decreases dopamine release in the NAC²⁸ (FIG. 8). With respect to dopamine terminals in the NAC, the (+) and (–) enantiomers may have pre- and post-synaptic actions, respectively, that equally contribute to the behavioral efficacy of the racemic compound. It should also be noted that, in contrast to the racemate, both enantiomers produce a small decrease in responding for water (FIG. 7), suggesting that the racemate may be more selective and have a higher therapeutic index than either of the enantiomers.

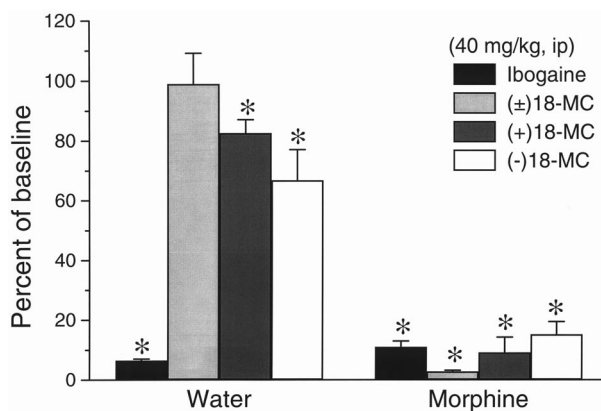


FIGURE 7. Comparison of the acute effects of ibogaine, (±)-18-MC, (+)-18-MC and (–)-18-MC on morphine self-administration and on responding for water.

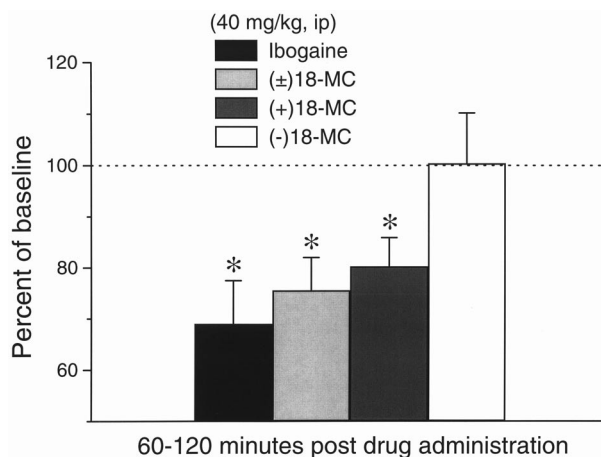


FIGURE 8. Comparison of the effects of ibogaine, (±)-18-MC, (+)-18-MC and (-)-18-MC on extracellular levels of dopamine in the nucleus accumbens; effects shown during the second hour after administration, when the effects were largest.

The results of a receptor screen comparing the binding affinities of 18-MC to those of ibogaine and noribogaine are shown in TABLE 1. Consistent with previous studies,²⁹⁻³⁸ ibogaine and noribogaine have low micromolar affinities for kappa and mu opioid receptors, NMDA receptors, 5HT-3 receptors, sigma-2 sites, sodium

TABLE 1. Affinities (μM Ki) of (±)-18-MC, ibogaine and noribogaine for receptor sites possibly mediating therapeutic and side effects

Ligand		Tissue	(±)-18-MC	Ibogaine	Noribogaine
Therapeutic Effect					
Kappa opioid	[³ H]-U69593	calf cortex	5.1 ± 0.50	2.2 ± 0.10	0.61 ± 0.015
Mu opioid	[³ H]-DAGO	calf cortex	1.1 ± 0.30	2.0 ± 0.15	0.68 ± 0.016
Delta opioid	[³ H]-DPDPE	calf caudate	3.5 ± 0.05	>10	5.2 ± 0.64
5-HT3	[³ H]-GR-65,630	NG-108 cells	3.8 ± 0.067	2.6 ± 0.23	>100
Side Effects					
NMDA	[³ H]-MK801	bovine cortex	>100	3.1 ± 0.30	15 ± 2.0
M1	[³ H]-pirenzepine	calf cortex	32 ± 3	16 ± 1.0	15 ± 1.0
M2	[³ H]-QNB	calf cortex	>100	31 ± 3.4	36 ± 3.7
Sodium channel	[³ H]-BTX-B	bovine cortex	6.4 ± 0.68	3.6 ± 0.35	17 ± 0.6
Sigma 2	[³ H]-DTG	calf hippocampus	13 ± 1.2	0.4 ± 0.036	19 ± 1.3
5-HT uptake	[³ H]-paroxetine	bovine brain stem	>10	4.1 ± 0.83	0.57 ± 0.083

channels and the serotonin transporter; it should also be noted that functional studies^{39,40} have indicated that ibogaine is a noncompetitive antagonist at nicotinic receptors, acting perhaps as an open channel blocker that is not revealed in binding studies.

The binding profile of 18-MC is somewhat different than that of ibogaine or nor-ibogaine. 18-MC has low micromolar affinities at all three opioid receptors and at 5HT-3 receptors but no affinity at NMDA receptors or the serotonin transporter. It seems unlikely, in view of the low affinities, that any of these actions could be responsible for "therapeutic" effects lasting a day or longer. However, preliminary findings (M. Fleck, personal communication) from patch-clamp recordings of adrenal chromaffin cells have suggested that 18-MC, like ibogaine, may have a nanomolar affinity for nicotinic channels—and perhaps this action could be relevant to prolonged therapeutic effects. Very low affinities at other sites may be responsible for 18-MC's potentially high therapeutic index compared to ibogaine. Actions of ibogaine at muscarinic (M1 and M2) receptors and at sodium channels may mediate its cardiovascular toxicity (bradycardia); 18-MC's affinity is at least twofold less than that of ibogaine at all of these sites. Ibogaine's action at sigma-2 sites has been linked to its neurotoxicity,⁴¹ and 18-MC's affinity at this site is many times less than that of ibogaine. We have previously suggested that the hallucinogenic effect of ibogaine may be due to serotonin release, and because 18-MC does not affect serotonin uptake or release, we predict that it will not be hallucinogenic.²⁷

Using gas chromatography-mass spectrometry, 18-MC has been measured in plasma and tissues of rats.⁴² Similar to ibogaine (Hough *et al.*, unpublished results), analysis of plasma 18-MC levels after i.v. administration indicated that 18-MC has a short initial half-life of 5–10 minutes and a terminal half-life of about 100 minutes. After i.p. and p.o. administration, analysis of tissues showed that 18-MC is highly sequestered in fat,⁴² again analogous to previous observations with ibogaine.⁴³ In absolute terms, even fat levels of 18-MC are low and the total amount of 18-MC measured in tissues accounts for less than 10% of the administered dose. This suggests that 18-MC, like ibogaine,^{33,34} is rapidly converted to an active metabolite. However, in contrast to ibogaine, which is also active itself, 18-MC itself may lack intrinsic activity and all of its effects may be mediated by one or more metabolic products. Thus while local administration of ibogaine into the nucleus accumbens mimics the effects of systemic administration of ibogaine on dopamine release,⁴⁴ local administration of 18-MC into the nucleus accumbens has no effect on dopamine release (Maisonneuve and Glick, unpublished results). Nevertheless, the deposition of 18-MC in fat could contribute to its prolonged duration of action by serving as a long-term depot of precursor for conversion to the active moiety.

In rats, moderate doses (20–40 mg/kg) of ibogaine induce whole body tremors and high doses ($\pm$ 100 mg/kg) result in degeneration of cerebellar Purkinje cells.^{9–11} In contrast, moderate doses (40 mg/kg) of 18-MC induce no tremors;¹³ rats appear completely normal, their locomotor activity not being altered for at least three hours.⁴² Importantly, even multiple high doses (100 mg/kg) of 18-MC do not damage the cerebellum.¹³ These latter results are consistent with 18-MC's relatively low affinity for sigma-2 sites compared to ibogaine⁴¹ (TABLE 1).

Anecdotal reports have suggested that, in people, ibogaine might have some cardiovascular toxicity attributable to a decrease in heart rate. In this laboratory, in

studies of awake and freely moving rats implanted with femoral artery catheters, high doses (100–200 mg/kg) of ibogaine decreased heart rate (without altering blood pressure) while moderate (40 mg/kg) doses had no effect. However, even high doses (200 mg/kg) of 18-MC had no effect.⁴²

DISCUSSION

Like ibogaine, 18-MC produces anti-addictive effects in several animal models of drug self-administration and also^{45,46} attenuates signs of withdrawal in opiate dependent rats.⁴⁷ However, 18-MC appears to be potentially much safer than ibogaine. Even at high doses, 18-MC does not mimic ibogaine in producing neurotoxic (Purkinje cells in cerebellum) or cardiovascular (bradycardia) effects. Moreover, acutely, 18-MC is more selective than ibogaine in that drug self-administration can be reduced without altering responding for a non-drug reinforcer (water). We are beginning to understand how 18-MC, as well as ibogaine, alters sensitivity to self-administered drugs. The 18-MC-induced downward shift in the dose-response curve for morphine self-administration suggests that 18-MC decreases the efficacy of morphine to function as a reinforcer. 18-MC may increase the activity of homeostatic mechanisms that control or limit morphine intake, effectively decreasing the “hedonic set point.”^{48,49}

18-MC's mechanism of action is still unclear. It has affinities for all three opioid receptors and perhaps its mechanism involves concomitant actions at all three sites. Such a mechanism would be consistent with reports that μ antagonists,⁵⁰ δ antagonists,^{51,52} and κ agonists⁵³ all modulate morphine and cocaine self-administration. However, all of these affinities are in the micromolar range and this is difficult to reconcile with the fact that 18-MC is behaviorally effective for 24–48 hours, when plasma and brain levels are very low. Moreover, 18-MC has effects that are incompatible with it being either an agonist or an antagonist at μ receptors. That is, in preliminary studies, 18-MC, like ibogaine,⁵⁴ was found to have very little or no analgesic efficacy resembling that of a μ agonist and, in contrast to what would be expected of a μ antagonist, both drugs^{46,47} attenuate naltrexone-precipitated withdrawal signs in morphine-dependent rats. It seems very likely, in view of its short half-life, that at least part of 18-MC's pharmacology, like that of ibogaine,^{17,55} is attributable to one or more active metabolites. 18-MC's prolonged effects might be due to its deposition in fat, with its slow release and conversion into active moieties occurring over a long period of time.

Another liability regarding the development of ibogaine is related to the fact that it has hallucinogenic properties. Until clinical trials are conducted, it will not be known whether or not 18-MC has this effect. Ibogaine elicits large increases in extracellular levels of serotonin in the brain,²⁷ and we have proposed that this action might be responsible for its hallucinogenic activity. Because 18-MC produces no change in brain serotonin levels,⁴² we have predicted that 18-MC will lack hallucinogenic activity.

In conclusion, the available evidence suggests that 18-MC could become a safe and effective treatment for multiple forms of drug abuse. Further investigation of its mode of action, as well as that of ibogaine, should provide a rational basis for designing novel agents with improved efficacy and safety. The possibility that a

single agent might have broad anti-addictive efficacy certainly has important implications for the neurobiology of drug addiction. If 18-MC's therapeutic potential is substantiated in the clinic, at least one African shrub will have left a very significant legacy.

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